REMARKS/ARGUMENTS

Applicants note that the amendment filed January 29, 2002, has been entered.

The Examiner has also stated that an amendment filed February 12, 2002, was entered. Applicants have no record of such an amendment and request clarification regarding this matter.

Applicants also note that the election of Group I, claims 1-5, 9, 10, 14-16, 20, 27, 29-31 and 39-42 has been acknowledged. Applicants further note that the drawings filed February 29, 2002, have been accepted by the Examiner.

Claims 1-46 were previously pending in this application.

Claims 6-8, 11-13, 17-19, 21-26, 28, 32-38, and 43-46 were withdrawn from further consideration under 37 C.F.R. § 1.142(b) as being drawn to a non-elected invention.

Claims 9, 14, 40, and 41 have been allowed.

Thus, claims 1-5, 10, 15-16, 20, 27, 29-31, 39 and 42 are currently pending in this application.

Amendments to the Claims

Claims 1, 5, 16, 27, and 29 have been amended. Support for the amendments to claims 1 and 5 can be found in the specification as originally filed at page 4, first full paragraph, third sentence. Support for the amendment to claim 16 can be found at page 1, first paragraph, second and third sentences, and page 4, last paragraph. Claims 27 and 29 have been amended to delete matter.

Previously withdrawn claims 6-8, 11-13, 17-19, 21-26, 28, 32-38, and 43-46 have been canceled without waiver or prejudice of subject matter contained therein. In addition, claims 3-4, 10, 15, 20, 39, and 42 have been canceled without waiver or prejudice of subject matter contained therein. Applicants reserve the right to pursue the subject matter of these claims in this or a related future application.

Claims 47-52 have been added. Support for these new claims can be found in the specification as originally filed; hence, the Examiner will appreciate that no new matter is being added by these amendments. Specifically, support for the newly added claims can be found at p.29, in the first and second paragraphs.

Claim Objecti ns

Claims 20, 27, and 29-31 were objected to because it was alleged that these claims were directed to non-elected inventions.

Claim 20 has been cancelled without waiver or prejudice of the subject matter contained therein and claim 27, from which claims 30 and 31 depend, and claim 29 have been amended to recite only the elected inventions of the restriction requirement.

With the entry of the amendment hereinabove, Applicants aver that this ground for objection has been overcome. Accordingly, Applicants respectfully request that this rejection be withdrawn and the Office Action mailed April 25, 2003 be reconsidered.

Claim 29 was objected to under 37 C.F.R. § 1.75(c) as being in improper form.

Without acquiescing to the propriety of this objection, claim 29 has been amended. With the instant amendment to these claims, Applicants aver that they have overcome this ground for objection. Thus, Applicants respectfully request that this rejection be withdrawn and the Application reconsidered.

Claim Rejections

(a) ***Rejections under 35 U.S.C. § 101***

Claims 1-5 were rejected under 35 U.S.C. § 101 because it is alleged that these claims are directed to non-statutory subject matter.

Claims 3 and 4 have been canceled without waiver or prejudice of the subject matter contained therein, and claims 1 and 5 have been amended to recite "a nucleic acid molecule separated from its natural source." As stated earlier, support for this amendment can be found at page 4, first full paragraph, third sentence.

With the entry of this amendment, Applicants aver that this ground for rejection has been overcome. Accordingly, Applicants respectfully request that this rejection be withdrawn and the Office Action mailed April 25, 2003 be reconsidered.

(b) ***Rejections under 35 U.S.C. § 112, first paragraph***

(i) Claims 3, 4, 10, 15, 39, and 42 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly not enabling a person of ordinary skill in the art to make and/or use the invention commensurate in scope with the claims.

Applicants have canceled claims 3, 4, 10, 15, 39, and 42 without waiver or prejudice of the subject matter contained therein. Applicants reserve the right to pursue the subject matter of these claims in this or a related future application.

Accordingly, the Examiner's rejection has been rendered moot.

(ii) Claims 16, 20, 27, 30 and 31 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly "containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention" (Office Action, p. 4, third paragraph).

Amended claim 16 recites a therapeutic composition comprising a nucleic acid molecule, encoding an osteoactivin protein comprising SEQ ID NO:2 or comprising amino acids 23-572 of SEQ ID NO:2, or a biologically active polypeptide fragment thereof, wherein said osteoactivin protein stimulates bone differentiation. Claim 20 has been canceled without waiver or prejudice. Currently amended claim 27 recites a method for stimulating bone formation in a mammal, comprising administering to said mammal a therapeutically effective amount of a therapeutic composition comprising a nucleic acid molecule encoding an osteoactivin protein, or a biologically active polypeptide fragment thereof, wherein said osteoactivin protein stimulates bone differentiation. Claims 30 and 31 depend on claim 27 as currently amended, and thus contain all of its limitations.

The Examiner states that the specification, the prior art, and the post-filing art, present insufficient evidence to lead one of skill in the art to conclude that expression of exogenous osteoactivin would stimulate bone growth. The Examiner has cited the reported findings of Weterman et al. (*Int. J. Cancer,* **60**:73, 1995), Sanicola-Nadel et al. (WO 97/44460) and Anderson et al. (*Nature Genetics*, **30**:81, 2002) to express doubt as to whether osteoactivin stimulates osteoblast function and bone differentiation.

In response to the Examiner's cited references, Applicants respectfully submit that these references are focused on cells or conditions different from Applicants' claimed invention: Weterman's focus is on melanoma cells, Sanicola-Nadel's on kidney cells, and Anderson's on pigmentary glaucoma. It is not possible to determine whether osteoactivin has a role in bone differentiation from these references because they have simply not considered bone cell development. The absence of a report of defects in bone cell development in references that do not even consider bone cell development as part of their studies cannot be construed as evidence that osteoactivin does not stimulate bone cell development. Thus, the lack of information regarding a role for osteoactivin in bone cell differentiation from studying melanocytes, kidney cells or retinal cells in these references individually, or taken together, cannot be taken to mean that osteoactivin does not have a role in bone cell differentiation.

Applicants have provided support in the specification of the instant Application as originally filed that osteoactivin can stimulate bone cell differentiation. For example, Applicants have shown that osteoactivin is expressed at the highest levels in osteoblasts, the cells that line bone surfaces and are involved in bone matrix production. Furthermore, osteoactivin is overexpressed in osteopetrotic rats which have more bone than normal rats (*see* p. 21, second paragraph; Fig. 4). Moreover, antibodies against osteoactivin inhibit calcium deposition by cultured osteoblast cells (*see* p.51, Example 13). These findings have also been supported by the art. Safadi, F. et al. have shown intense staining of osteoactivin mRNA lining bone surfaces *in vivo* (*J Cell Biochem.* **84**:12-26, 2001). In addition, Hadjiargyrou, M. et al. (J. *Biol. Chem.* **277**:30177-30182, 2002) have shown that osteoactivin expression increased with time in a fracture repair model reaching a maximum at 2 weeks post-fracture.

In addition, Applicants provide herewith an unpublished manuscript entitled "Effects of Modulating of Osteoactivin Expression on Osteoblast Differentiation" by Selim, A. et al. attached as Appendix A, which supports Applicants' claimed invention. In this manuscript, the effects of loss and gain of expression of osteoactivin on osteoblast development are studied using different conventional markers, such as alkaline phosphatase activity, osteocalcin expression, calcium deposition, and nodule formation. Loss of expression of osteoactivin using antisense oligonucleotides, is shown to result in significant inhibition of these osteoblast differentiation

markers (*see* p.11, last paragraph, Figs. 3-4 at p. 23-24). In striking contrast, gain of osteoactivin expression is shown to significantly induce these osteoblast differentiation markers, as well as Cbfa1, a "master" gene for osteoblast differentiation and development (*see* p.12, Figs. 7-8 at p. 26-27). Taken together these data indicate a critical role for osteoactivin in osteoblast differentiation.

The Examiner has also cited reviews by Orkin and Verma to raise concerns regarding gene therapy. Specifically, the Examiner alleges that not a single successful gene therapy protocol has been described in the art.

Contrary to the Examiner's position Applicants state that several successful examples of gene therapy existed before Applicants' filing, one of which is even acknowledged by the Examiner-cited Verma reference (*see* p. 242, left column, Clinical Trials). The first successful gene therapy on humans was performed in 1990 by researchers at the National Institutes of Health (Blaese, R.M. et al. *Science* **270**:475-480, 1995; Bordignon, C. et al. *Science* **270**:470-475, 1995). The then four-year old Ashanthi DeSilva was treated for adenosine deaminase (ADA) deficiency, a rare genetic disease in which children are born with severe immunodeficiency and are prone to repeated serious infections. Since then other examples of successful gene therapy have been reported (for three examples *see*, Onodera et al. *Blood* **91**:30-36, 1996; Grossman, M. et al. *Nat.Genet.* **6**:335-341, 1994; and Lee, J. Y. et al. *Hum. Gene Ther.* **13**:1201-1211, 2002). Therefore, the Examiner's statement that not a single gene therapy protocol has been described in the art or been successful is inaccurate. As a courtesy to the Examiner, the five Applicant-cited references in this paragraph are attached as Appendix C.

The Examiner has alleged that Applicants have provided no teaching regarding target cells and the delivery of the nucleic acids of the invention. Applicants respectfully disagree. Applicants' specification provides ample guidance to one of ordinary skill in the art regarding target cells and the delivery of nucleic acid molecules (*e.g., see* pages 34-36, especially page 34, first paragraph). Furthermore, as evidenced by the references listed above, it is clear that there was sufficient guidance in the art regarding successful gene therapy as early as 1990.

Thus, Applicants aver that the grounds for this rejection under 35 U.S.C. 112, first paragraph, have been overcome. Accordingly, Applicants respectfully request that this rejection be withdrawn and the Office Action mailed April 25, 2003 be reconsidered.

(c) ***Rejections under 35 U.S.C. § 102(a)***

(i) Claims 1-5 were rejected under 35 U.S.C. § 102(a) as being anticipated by Xu et al., GenBank® Acc. No. AF184983, 21 October 1999 (Office Action mailed April 25, 2003, page 14, last two paragraphs).

Applicants respectfully traverse this rejection.

Applicants submit herewith a Declaration under 37 C.F.R. § 1.132 (In re Katz Declaration) as Appendix B, which establishes that the Xu et al. reference describes Applicants own work. Additionally, this Declaration explains that the reference is authored by the inventors of this patent application, as well as additional individuals who are not co-inventors.

Thus, Applicants respectfully assert that the ground for this rejection as it relates to claims 1, 2, and 5 has been overcome. This rejection is rendered moot as it relates to claims 3 and 4 upon entry of the amendment hereinabove. Accordingly, Applicants request that this rejection be withdrawn and the Office Action mailed April 25, 2003 be reconsidered.

(ii) Claim 3 stands rejected under 35 U.S.C. § 102(a) as being anticipated by Bachner, GenBank® Acc. No. AJ251685, January 7, 2000 (Office Action mailed April 25, 2003, page 15, ll. 1-2).

Claim 3 has been canceled without waiver or prejudice of the subject matter contained therein. Thus, this rejection has been rendered moot. Accordingly, Applicants respectfully request that this rejection be withdrawn and the Office Action mailed April 25, 2003 be reconsidered.

(d) ***Rejections under 35 U.S.C. § 102(b)***

Claims 3, 10, 15, 16 and 20 were rejected under 35 U.S.C. § 102(b) as being anticipated by Sanicola-Nadel et al. (WO 97/44460).

The Examiner purports that Sanicola-Nadel et al. disclose a rat-derived nucleic acid molecule that is related to nucleotides 115-1830 of SEQ ID NO:1 of the instant application.

Claims 3, 10, 15 and 20 have been canceled without waiver or prejudice of the subject matter contained therein. Claim 16 has been amended to recite the rat osteoactivin amino acid sequence disclosed in the instant application, namely SEQ ID NO:2 or comprising amino acids 23-572 of SEQ ID NO:2.

With the instant amendments, the grounds for the rejection of the claims under 35 U.S.C. § 102(b) have been overcome. Accordingly, Applicants respectfully request that this rejection be withdrawn and the Office Action mailed April 25, 2003 be reconsidered.

(e) ***Rejections under 35 U.S.C. § 102(e)***

Claims 3, 10, 15, 16 and 20 were rejected under 35 U.S.C. § 102(e) as being anticipated by Strachan et al., U.S. Patent No. 6,242,419 (Office Action mailed April 25, 2003, page 16, second paragraph).

The Examiner alleges that Strachan et al. disclose a nucleic acid molecule from the mouse that corresponds to SEQ ID NO:7 (mouse nmb) of the instant application.

Applicants have canceled claims 3, 10, 15 and 20 without waiver or prejudice of the subject matter contained therein. Claim 16 has been amended to recite the rat osteoactivin sequence comprising SEQ ID NO:2 or comprising amino acids 23-572 of SEQ ID NO:2.

Thus, in view of these amendments, the 35 U.S.C. § 102(e) rejections have been overcome. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Conclusi n

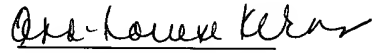
In view of the amendment and arguments made above, Applicants submit that the outstanding rejections of record have been overcome, and that the claims are in condition for allowance. Thus, Applicants respectfully request that a timely Notice of Allowance be issued in this case.

No fees are believed to be due; however, if fees are due, the Office is authorized to charge any fees or credit any overpayments to our Deposit Account No. 08-0219.

Should the Examiner consider that a discussion would be helpful in moving the application to allowance, the Examiner is respectfully requested to contact the undersigned at the address below.

Respectfully submitted,

Date: July 25, 2003



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